IN THE CLAIMS

Please amend the claims as follows. The following claim set is intended to reflect amendment of previously pending claims 1, 12, 13 and 14. The specific amendments to individual claims are detailed in the following marked up set of claims.

1. (Currently Amended) A method of determining the presence of a mutation in a target polynucleotide, comprising the steps of:

(a) providing at least two identical polynucleotide probe arrays, each array comprising perfect match probes and mismatch probes, wherein each probe comprises a double stranded region and a single-stranded n-mer overhang region such that the overhangs in each array constitute a complete set of n-mers;

(b) hybridizing the target polynucleotide to said overhangs of probe polynucleotides in one array to generate a target hybridization pattern;

(c) hybridizing a reference polynucleotide to said overhangs of probe polynucleotides in a second array to generate a reference hybridization pattern; and

(d) determining the presence of a mutation in the target polynucleotide by normalizing intensity differences of hybridized perfect match probes in the reference and target hybridization patterns, comparing intensity differences of mismatch probes in the reference and target hybridization patterns and determining whether a mutation is present in the target polypeptide;

wherein normalizing intensity differences comprises dividing each perfect match probe hybridization intensity by a sum of hybridization intensities for all related single base mismatch probes plus a hybridization intensity for the perfect match probe

~~wherein the method has a false positive rate of less than 1 per 3900 bp~~.

2. (Original) The method of claim 1, wherein in step b), the hybridized target polynucleotide is ligated to the probe.

3. (Original) The method of claim 1, wherein in step c), the hybridized reference polynucleotide is ligated to the probe.

4. (Original) The method of claim 1, wherein the overhangs have free 5'-ends.

5. (Original) The method of claim 1, wherein the overhangs have free 3'-ends.

6. (Original) The method of claim 1, wherein the n-mer comprises from about 4 to about 50 nucleotides.

7. (Original) The method of claim 1, wherein the mutation is a substitution mutation.

8. (Original) The method of claim 1, wherein the mutation is a deletion mutation.

9. (Previously Amended) The method of claim 1, wherein the mutation is an insertion mutation.

10. (Original) The method of claim 1, in which said target polynucleotide is selected from the group consisting of: a cystic fibrosis transmembrane conductance regulator gene, a p53 gene, a mitochondrial DNA, or an HIV gene.

11. (Previously Amended) The method of claim 1, wherein the arrays are arranged in parallel.

12. (Currently Amended) A method of determining whether two or more target polynucleotides are identical, comprising the steps of:

(a) providing at least two identical polynucleotide probe arrays, each array comprising perfect match probes and mismatch probes, wherein each probe comprises a double stranded region and a single-stranded n-mer overhang region such that the overhangs in

each array constitute a complete set of n-mers~~, wherein each n-mer is at least 8 nucleotides in length~~;

(b) hybridizing first target polynucleotide to said overhangs of probe polynucleotides in one array to generate a first hybridization pattern;

(c) hybridizing second target polynucleotide to said overhangs of probe polynucleotides in a second array to generate a second hybridization pattern; and

(d) normalizing intensity differences of hybridized perfect match probes in the first and second hybridization patterns, comparing intensity differences of mismatch probes in the first and second hybridization patterns and determining whether two or more target polynucleotides are identical;

wherein normalizing intensity differences comprises dividing each perfect match probe hybridization intensity by a sum of hybridization intensities for all related single base mismatch probes plus a hybridization intensity for the perfect match probe.

~~wherein the method has a false positive rate of less than 1 per 3900 bp~~.

13. (Currently Amended) The method of claim 12, wherein in step b), the hybridized first target polynucleotide is ligated to the probe.

14. (Currently Amended) The method of claim 12, wherein in step c), the hybridized ~~reference~~ second target polynucleotide is ligated to the probe.

15. (Original) The method of claim 12, wherein the overhangs have free 5'-ends.

16. (Original) The method of claim 12, wherein the overhangs have free 3'-ends.

17. (Original) The method of claim 12, wherein the n-mer comprises from about 4 to about 50 nucleotides.

18. (Previously Amended) The method of claim 12, wherein the arrays are arranged in parallel.

REMARKS

Applicant has reviewed and considered the Office Action mailed on January 16, 2003, and the documents cited therewith. Claims 1, 12, 13 and 14 are amended to clarify the subject matter to which applicants are entitled. In particular, claims 1 and 12 have been amended to clarify that the array comprises perfect match and mismatch probes in step (a). Support for this subject matter can be found in the specification, for example, at Page 27, Line 11 to Page 28, Line 30, the Examples (e.g., Examples 2 and 5) and the Figures (e.g., Figure 10a and 10b). Claims 1 and 12 have also been amended to clarify that the intensity differences of the different target or reference polynucleotide hybridization patterns for the perfect match probes are normalized in step (d). Support for this subject matter can be found in the specification, for example, at Page 23, Lines 10-18; Page 27, Line 11 to Page 28, Line 30; the Examples (e.g., Examples 2 and 5); and the Figures (e.g., Figure 10a and 10b). Claims 1 and 12 have also been amended to clarify that the intensity differences of the different target or reference polynucleotide hybridization patterns for the mismatch probes are compared in step (d). Support for this subject matter can be found in the specification, for example, at Page 27, Line 11 to Page 28, Line 30; the Examples (e.g., Examples 2 and 5); and the Figures (e.g., Figure 10a and 10b). Claim 1 has been amended to clarify that the method further involves determining whether a mutation is present in a target polynucleotide and claim 12 has been amended to clarify that the method further involves determining whether two or more target polynucleotides are identical. Support for this subject matter can be found in the preambles of claims 1 and 12, respectively, as filed. Claim 12 has been amended to delete language relating to "wherein each n-mer is at least 8 nucleotides in length." Support for this amendment can be found in claim 12, as filed. The language of claims 13 and 14 has been amended to reference first and second target polynucleotides. Antecedent basis for these amendments can be found in claim 12. Applicant submits that no new matter has been added by these amendments.

Information Disclosure Statement

Applicant respectfully requests that copies of the 1449 Forms listing all documents that were submitted with the Information Disclosure Statements filed on February 14, 2000 and October 15, 2002, marked as being considered and initialed by the Examiner, be returned with the next official communication.

§112 Rejection of the Claims

Claims 12-18 were rejected and the specification was objected to under 35 U.S.C. § 112, first paragraph, as containing subject matter that allegedly was not described in the specification at the time the application was filed. The Examiner has indicated that language "wherein each n-mer is at least 8 nucleotides in length" is not supported by the specification because no upper limit is specified. While applicants believe that the application clearly provides a written description of this subject matter, to advance the prosecution of the claims, language relating to "wherein each n-mer is at least 8 nucleotides in length" has been deleted from claim 12. Accordingly, this rejection under 35 U.S.C. § 112, first paragraph, is rendered moot. Withdrawal of these written description rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

§103 Rejection of the Claims

Claims 1-18 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Cantor et al. (U.S. Patent No. 5,631,134, filed June 5, 1995) in view of Southern (U.S. Patent No. 5,700,637, filed April 19, 1994), Yershov et al. (Proc. Natl. Acad. Sci., USA, 93: 4913-4918 (1993)) and Fodor et al. (U.S. Patent No. 5,800,992). The Examiner has stated that the phrase "wherein the method has a false positive rate of less than 1 per 3900 bp," is not a method step and is inherently taught by the prior art.

Applicant submits that the test for obviousness under § 103 must take into consideration the invention as a whole; that is, one must consider the particular problem solved by the combination of elements that define the invention. *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985). The Examiner must also recognize and consider not only the similarities but also the critical differences between the claimed

invention and the prior art. *In re Bond*, 910 F.2d 831, 834, 15 U.S.P.Q.2d (BNA) 1566, 1568 (Fed. Cir. 1990), *reh'g denied*, 1990 U.S. App. LEXIS 19971 (Fed. Cir. 1990). Hindsight must also be avoided. *Id.* The Examiner cannot use the Appellant's structure as a "template" and simply select elements from the references to reconstruct the claimed invention. *In re Gorman,* 933 F.2d 982, 987, 18 U.S.P.Q.2d (BNA) 1885, 1888 (Fed. Cir. 1991).

Moreover, the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversing rejection because alleged inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

Applicant maintains that the claims are novel and non-obvious in view of the prior art. However, language relating to "wherein the method has a false positive rate of less than 1 per 3900 bp," has been deleted to advance the prosecution of this application.

Accordingly, claim 1 is directed to a method of determining the presence of a mutation in a target polynucleotide without sequencing the target polynucleotide. The steps recited in claim 1 include (a) providing at least two identical polynucleotide probe arrays, each array comprising perfect match probes and mismatch probes, wherein each probe comprises a double stranded region and a single-stranded n-mer overhang region such that the overhangs in each array constitute a complete set of n-mers; (b) hybridizing the target polynucleotide to said overhangs of probe polynucleotides in one array to generate a target hybridization pattern; (c) hybridizing a reference polynucleotide to said overhangs of probe polynucleotides in a second array to generate a reference hybridization pattern; and (d) determining the presence of a mutation in the target polynucleotide by normalizing intensity differences of hybridized perfect match probes in the reference and target hybridization patterns, comparing intensity differences of mismatch probes in the reference and target hybridization patterns and determining whether a mutation is

present in the target polypeptide; wherein normalizing intensity differences comprises dividing each perfect match probe hybridization intensity by a sum of hybridization intensities for all related single base mismatch probes plus a hybridization intensity for the perfect match probe.

Claim 12 is directed to a method of determining whether two or more target polynucleotides are identical, wherein the method has a false positive rate of less than 1 per 3900 bp. Step (a) of claim 12 is the same as step (a) of claim 1. Step (b) of claim 12 involves hybridizing first target polynucleotide to the overhangs of probe polynucleotides in one array to generate a first hybridization pattern. Step (c) of claim 12 involves hybridizing second target polynucleotide to the overhangs of probe polynucleotides in a second array to generate a second hybridization pattern. Step (d) of claim 12 involves normalizing intensity differences of hybridized perfect match probes in the first and second hybridization patterns, comparing intensity differences of mismatch probes in the first and second hybridization patterns and determining whether two or more target polynucleotides are identical; wherein normalizing intensity differences comprises dividing each perfect match probe hybridization intensity by a sum of hybridization intensities for all related single base mismatch probes plus a hybridization intensity for the perfect match probe.

Applicant respectfully submits that the present claims are not disclosed by the cited combination of references. For example, none of the references provides a teaching of a hybridization method that involves normalizing the intensity differences of perfect match probes by dividing each perfect match probe hybridization intensity by a sum of hybridization intensities for all related single base mismatch probes plus a hybridization intensity for the perfect match probe. Similarly, none of the cited references teach comparing intensity differences of mismatch probes.

Cantor et al. (U.S. Patent 5,631,134) describes the problems facing sequencing by hybridization including poor levels of discrimination, sequence ambiguities and the like. *See* col. 2, line 37 to col. 3, line 21. However, Cantor et al. provide no teaching of a method that involves normalizing the hybridization signal as described in the present claims and comparing intensity differences of mismatch probes. Similarly, none of Southern (U.S. Patent 5,700,637), Yershov et al. (Proc. Natl. Acad. Sci., USA, 93: 4913-4918 (1993)) or Fodor et al. (U.S. Patent No. 5,800,992) discloses such normalizing and comparing steps.

Accordingly, the combination of Cantor et al. (U.S. Patent No. 5,631,134) in view of Southern (U.S. Patent No. 5,700,637), Yershov et al. (Proc. Natl. Acad. Sci., USA, 93: 4913-4918 (1993)) and Fodor et al. (U.S. Patent No. 5,800,992) does not disclose or teach the subject matter of claims 1-18. Applicant respectfully requests withdrawal of this rejection under 35 U.S.C. § 103(a).

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (516) 795-6820 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

KEVIN L. GUNDERSON ET AL.

By their Representatives,

SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.
P.O. Box 2938
Minneapolis, MN 55402
(516) 795-6820

Date Apr. 16, 2003 By Robin A. Chadwick
Robin A. Chadwick
Reg. No. 36,447

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Box AF, Commissioner of Patents, Washington, D.C. 20231, on this 16th day of April, 2003.

Candis B. Buending
Name

Signature